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Base-controlled selective construction of polysubstituted dihydrofuran and furan derivatives through an I_2-mediated cyclization

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ABSTRACT

A base-controlled formal [3 + 2] cycloaddition of 1,3-dicarbonyl compounds to enones *via* an I_2-mediated cyclization was reported. Highly functionalized dihydrofurans and furans were selectively obtained under I_2/DMAP and I_2/DBU conditions in the cyclization step, respectively.

Introduction

Dihydrofuran and furan skeletons constitute a class of biologically active compounds that are found in many natural products as well as therapeutic agents such as neotanshinlactone,[1] evodone,[2] coumestans,[3] clerodin,[4] azadirachtin,[5] and austocystin A[6] (Fig. 1). Their broad bioactivities have inspired chemists to develop versatile efficient synthetic methods. The radical cyclic addition reaction of active methylene compounds with alkenes promoted by transition metal salts such as manganese (III) acetate[7], cerium (IV) ammonium nitrate,[8] Ag (I), and Cu (II)[9] represents one of the mostly used method. However, excess transition metal salts have to be used as oxidants. Furthermore, when electron-poor alkenes were employed as the substrates, the product **I** was obtained selectively (Scheme 1) with the carbon of 1,3-dicarbonyl compounds added at the α-position of electron-poor alkenes. A reversed regioselective radical cyclic addition leading to product **II** was rather rare (Scheme 1).[7a] The reaction of diazo compounds with alkenes/alkynes via organometallic catalysis have also attracted much attention.[10] But the chemoselectivity was usually poor. The formal [4 + 1] annulation of enones with ylides has been widely employed for the construction of heterocycles.[11] Nevertheless the control of the competitive formation of cyclopropane products is a thorny problem. Beside these methods, hypervalent iodine mediated annulation of 1,3-dicarbonyl compounds with alkenes for the construction of dihydrofurans have been explored.[12]

I_2 as an inexpensive, non-toxic, readily available reagent has been found significant application in organic transformations.[13] Most recently, we reported the preparation of four-membered ring heterocycles such as oxetane and azetidine derivatives through an I_2-mediated cyclization of the Michael adducts of malonates/amidomalonate with enones.[14] Herein, we would extend this method to the synthesis of five-membered ring heterocycles and demonstrated the preparation of polysubstituted dihydrofurans/-furans *via* the I_2-mediated annulation.

Results and discussion

To verify our hypothesis, Michael adduct **1aa** was chosen as the model substrate to react with I_2 under various conditions (Table 1). The reaction in DMF with K_2CO_3 as the base afforded the desired product **2aa** in 59% yield (Table 1, entry 1). Using Et_3N as the base, the reaction in dichloromethane gave the best yield among the four evaluated solvents (Table 1, entries 2–5). Further screening different bases for this transformation in CH_2Cl_2 revealed that pyridine and DABCO were not effective (Table 1, entries 7 and 8) and DMAP was the best base to afford **2aa** in 70% yield within 20 min (Table 1, entry and 6). Although NMI and Et_3N gave comparable yield with that of DMAP, much longer reaction time was needed (Table 1, entries 3 and 9). When the strong organic base DBU was introduced to the reaction, to our surprise, beside the formation of

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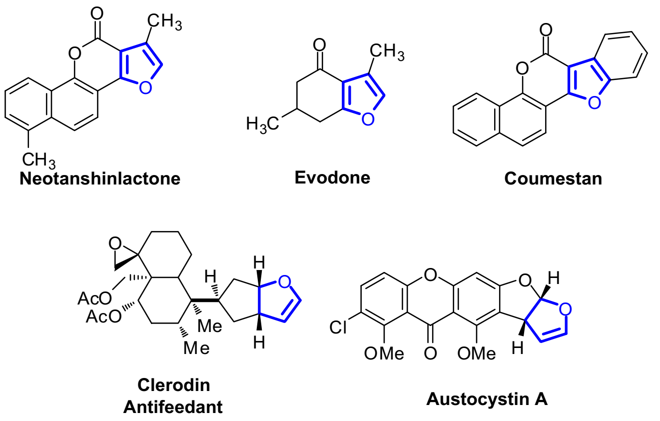
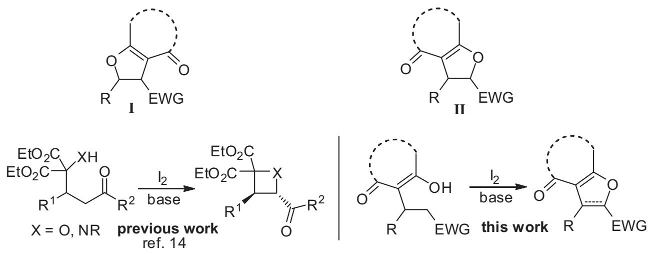


Fig. 1. Selective biologically active natural products bearing dihydrofuran/furan subunits.



Scheme 1.

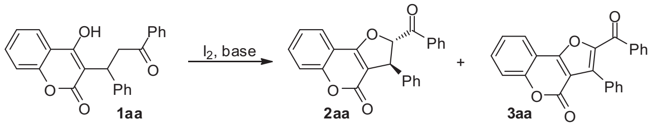
2aa a new product with slightly lower polarity was isolated in 21% yield, which was assigned as the furan product **3aa** through NMR analysis (Table 1, entry 10). The **3aa** might be generated from the **2aa** through further iodination and subsequent dehydroiodination, which implied at least 2 equiv of I_2 was needed in the transformation. When the amounts of I_2 and DBU were increased to 2.7 and 5.4 equiv, respectively, the yield of **3aa** was improved notably to 64% (Table 1, entry 11). It was noteworthy if DMAP was used as the base, even increasing the amounts of I_2 and DMAP to 2 and 4 equiv, respectively, no furan **3aa** was generated, which demonstrated that the choice of base was crucial to formation of **3aa** from **2aa**. The reaction of **1aa** with I_2/DBU in THF also gave a comparable yield of **3aa** (Table 1, entry 12). However, using CH_3CN or EtOH as the solvent the conversion was incomplete along with surplus of considerable amount of **2aa** even prolonging the reaction time to 10 h (Table 1, entries 13 and 14). Oxidation with stoichiometric amounts of DDQ, MnO_2[15] or oxidative dehydrogenation catalyzed-by Pd at high temperature for a long time[16] was the commonly used method for the transformation of dihydrofuran to furan. Herein we provided a new approach for this conversion under mild conditions.

It is interesting that the chemoselective conversion of **1aa** to **2aa** or **3aa** in the presence of I_2 is controlled by the base. As we know, tunable highly selective synthesis derived from the same reactants is a formidable challenge in organic synthesis.[17] In order to make this approach easier to operate, the possibility of constructing dihydrofurans/furans *via* a one-pot formal [3 + 2]-cycloaddition process involving a Michael addition and I_2-mediated cyclization was tried.

A mixture of 4-hydroxycoumarin, 1.1 equiv of chalcone, and catalytic amount of TEBAC (benzyl triethyl ammonium chloride) was refluxed in water overnight until the disappearance of 4-hydroxycoumarin, then I_2, 5 mL of CH_2Cl_2, and DMAP (or DBU) were added sequentially and the mixture was stirred at room temperature until the completion of reaction, furnishing **2aa** and **3aa** in 56% and 53% yield, respectively. No workup procedure or the purification of Michael addition mixture and no oxygen-free operation were required, which made the protocol very easy to operate. The generality of this formal [3 + 2]-cycloaddition for the synthesis of polysubstituted dihydrofurans/furans was evaluated with 4-hydroxycoumarin **4a** and various enones as the substrates (Tables 2 and 3).

For most cases, 4-hydroxycoumarin **4a** reacted with enones **5** under I_2/DMAP conditions leading to the corresponding dihydrofuran products **2** in moderate yields (Table 2). The reaction tolerated a range of various groups with different electronic demands on the

Table 1
Screening of the reaction conditions.[a]



Entry	Base	Solvent	**1aa**:I_2:base	Time (h)	Yield[b](%)	
					2aa	**3aa**
1	K_2CO_3	DMF	1:1.1:2.2	5	59	0
2	Et_3N	THF	1:1.1:2.2	3	62	0
3	Et_3N	CH_2Cl_2	1:1.1:2.2	3	67	0
4	Et_3N	EtOH	1:1.1:2.2	3	Trace	0
5	Et_3N	CH_3CN	1:1.1:2.2	3	51	0
6	**DMAP**	**CH_2Cl_2**	**1:1.1:2.2**	**0.5**	**70**	**0**
7	Pyridine	CH_2Cl_2	1:1.1:2.2	12	14	0
8	DABCO	CH_2Cl_2	1:1.1:2.2	12	17	0
9	NMI	CH_2Cl_2	1:1.1:2.2	2	64	0
10	DBU	CH_2Cl_2	1:1.1:2.2	1	30	21
11	**DBU**	**CH_2Cl_2**	**1:2.7:5.4**	**0.5**	**Trace**	**64**
12	DBU	THF	1:2.7:5.4	3	Trace	58
13	DBU	CH_3CN	1:2.7:5.4	10	19	23
14	DBU	EtOH	1:2.7:5.4	10	28	17

[a] A mixture of **1aa** (1 mmol), I_2, and base was stirred in 2 mL of solvent at room temperature.
[b] Isolated yield.